REMARKS

Claims 18, 23-25 and 27 are pending in the instant application. Applicants note the Examiner's withdrawal of the prior rejections under 35 U.S.C. §112, first paragraph, for lack of enablement and lack of written description, as well as the prior rejection under 35 U.S.C. §102. For reasons set forth below, Applicants contend that the two remaining rejections, both under 35 U.S.C. §103(a), should be withdrawn and the presently pending claims should be allowed to issue.

1. The Claims Are Not Obvious over Ishida et al. and Secondary References

Claims 18, 23-25, and 27 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Ishida *et al.*, (Nature Biotech. (1996) 14:745-750; hereinafter "Ishida *et al.*") in view of Does *et al.*, (Plant Mol. Biol. (1991) 17:151-153; "hereinafter "Does *et al.*"), Hiei *et al.*, (Plant Journal (1994) 6(2):271-282; hereinafter "Hiei *et al.*"), Armstrong *et al.*, (Theoretical and Applied Genetics (1992) 84:755-762; hereinafter "Armstrong *et al.*") and Ragot *et al.*. The Examiner's basis for this rejection is found in the June 25, 2004 Office Action[1], where the Examiner introduced the cited art and asserted the following rationale as establishing a *prima facie* case of obviousness:

> Ishida et al. teach the transformation of hybrid plants comprising the parental line of which are, a line suited for transformation (A188) and a line of interest (five different inbred lines) through the use of Agrobacterium (see pages 745-747). They do not teach selection of hybrid primary transformants having the integrated T-DNA or the back-crossing of selected hybrid primary transformants with the parental line of interest. They also do not teach the

[1] In each of the prior Office Actions the Examiner cites either directly or indirectly (i.e., through a chain of Office Actions) to the Office Action of June 25, 2006 as providing the foundation for this rejection under §103(a). Where the Examiner has clarified this rationale in subsequent Office Actions, that clarification is also presented.

selection of at least one transgenic individual derived from each backcrossing until an isotransgenic line is produced.

Does et al. teach a method of obtaining one integrated T-DNA in the genome of tobacco 10 weeks after transformation by using inverse polymerase chain reaction (IPCR) to amplify plant genomic DNA sequences flanking the known T-DNA sequences (see, pages 151-153).

Hiei et al. teach a method of producing transgenic rice plants by co-cultivation of monocotyledonous rice tissues with *Agrobacterium tumefaciens* and the analysis of the plant genomic DNA sequences flanking T-DNA using PCR (see, pages 279-281). They also report the use of a super binary vector that confers high frequencies of transformation.

Armstrong et al. teach the method of transforming cells of hybrid plants and the backcrossing of said plants to recurrent parent (see, pages 756-757). They disclose a backcrossing program initiated by establishing Type-II cultures from immature F_2 embryos from a sib-pollinated A188 x B73 plant. The regenerated plant from one F_2 culture was crossed with the recurrent parent (B73) to produce BC_1 populations. BC_1 plants were selfed and immature embryos were placed in culture was used to cross with the recurrent parent (B73) to produce BC_2 population. This procedure was repeated to produce a BC_3 population, which was simultaneously self-pollinated and backcrossed. Their results demonstrate the effectiveness of backcrossing in improving culture response to an elite variety. In addition, Armstrong et al. teach the use of RFLP analysis in identifying the locations and effects of the introgressed A188 chromosomal regions.

Ragot et al. teach the desirability of isogenic maize lines containing a gene of interest, but otherwise maintaining the genome of an elite agronomic line, including the use of transgenes conferring agronomic properties as the introgressed gene (see, page 45, second paragraph; page 46, third full paragraph; page 55, first paragraph).

Therefore it would have been obvious to one of ordinary skill in the art at the time the invention was made would to have used (sic) the method of Ishida et al. to transform hybrid plants and to modify that method by incorporating that of Does et al. and Hiei to assay the T-DNA integrated into the genome of said plants and furthermore, to use the backcrossing and RFLP method of Armstrong et al. to develop isotransgenic plants containing a desired transgene given the desirability of isogenic transgenic lines and success in obtaining them as taught by Ragot et al.

(See, Office Action of June 25, 2004, pages 16-17).

Although the Examiner has maintained the above rejection in each Office Action subsequent to the Action of June 25, 2004, it was not until the pending Office Action that the

Examiner further clarified this rationale.[2] Specifically, the Examiner asserted in the pending Office Action that:

> Does et al teach a method of obtaining T-DNA in the genome of plants to amplify plant genomic DNA sequences flanking the known T-DNA sequences (see page 16, 2nd paragraph). In addition, how the selection is performed does not affect the principle component of the claimed step, which is selecting for at least one individual which has T-DNA integrated into the genome of interest.
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> The examiner has provided references that provide evidence that it would have been obvious to one of ordinary skill in the art to use the cited references to make the claimed invention (see pages 15-18 of the Office Action mailed June 25, 2004). In fact, the teachings of Ragot et al are the motivation for one of skill in the art to combine the cited references because Ragot et al teach the desirability of isogenic maize lines containing a gene of interest and maintaining the genome of an elite agronomic line.

(See, Office Action of December 13, 2006, pages 4-5).

As pointed out in the previously-filed Responses, Applicants respectfully disagree with the Examiner and reiterate that the cited references, taken singly or in combination, fail to teach or suggest a limitation of the claims which is crucial to the success of the invention and otherwise fail to establish *prima facie* obviousness.

As the Examiner is aware, in order to establish a *prima facie* case of obviousness, three basic criteria must be met. First, the prior art reference (or references when combined) must teach or suggest all the claim limitations. (See, *In re* Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974)). Second, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. (See, *In re* Kahn, 441 F.3d 977, 986, 78 USPQ2d 1329, 1335 (Fed. Cir. 2006)). Finally, there must be a reasonable expectation of

[2] In each of the Office Actions issued between the June 25, 2004 and December 13, 2006 Actions, the Examiner failed to address the propriety of the claim of *prima facie* case obviousness, and instead argued that the Applicant's comments were irrelevant as directed to single references rather than to the combination of references as a whole, a contention that Applicants continue to vigorously traverse.

success. (See, Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200, 1207-08, 18 USPQ2d 1016, 1022-23 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991)).

As pointed out above, in order to establish a *prima facie* case of obviousness, the Examiner must identify how the cited art teaches or suggests all of the claim limitations. As Applicants have repeatedly argued, the cited art (either alone or in combination) does not teach or suggest the following claim limitation of Claim 18:

> b) selecting for at least one individual among said hybrid primary transformants which has said T-DNA integrated only into the genome of said line of interest, in order to obtain selected individual(s), wherein said selection is performed by isolation and identification of genomic sequences of the host adjacent to the T-DNA;

This limitation makes clear that the selection step not only identifies the presence of the transgene, but also selects only for only those plants where the transgene has integrated into a chromosome of the line of interest (a line that is recalcitrant or unsuited to transformation and has a transformation efficiency of zero to 1/100). In the absence of this selection step, it would be impossible to predict that the subsequent backcrosses would generate an isotransgenic maize line as claimed.

The Examiner has attempted to counter Applicant's position by contending that that Does *et al.* teaches such a selection method. In particular, the Examiner argues that the Does *et al.* teaches "a method of obtaining T-DNA in the genome of plants to amplify plant genomic DNA sequences flanking the known T-DNA sequences (see page 16, 2nd paragraph). In addition, how the selection is performed does not affect the principle component of the claimed step, which is selecting for at least one individual which has T-DNA integrated into the genome of interest." (See, Office Action of June 25, 2004, pages 16-17). In making this argument the Examiner ignores the fact that the system described in Does *et al.* (which only identifies T-DNA

after it has been excised from genomic DNA) cannot differentiate in which line the T-DNA had been integrated, and therefore cannot be used to select for integration of the transgene into the line of interest. Contrary to the Examiner's statement above, "how the selection is performed" does indeed "affect the principle component of the claimed step," particularly when the method described in Does *et al.* is incapable of achieving that principle component. Given the deficiency in the system described by Does et al., and the failure of any of the remaining pieces of art to supply the missing teaching, or to even suggest such a teaching, Applicants respectfully assert that the cited art fails to teach or suggest all of the claim limitations.

In order to satisfy the second criteria for establishing a *prima facie* case of obviousness, the Examiner must identify some suggestion or motivation to combine the cited references. Applicants point out, however, that the Federal Circuit has clearly stated that there can be no suggestion or motivation to combine a group of references if the proposed combination would render the subject matter disclosed in those references unsatisfactory for their intended purpose. (See, *In re* Gordon, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984)). Similarly, it is well established that if the proposed combination of references would change the principle of operation of the subject matter disclosed in those references, then the combined teachings of the references cannot be deemed sufficient to render the claims *prima facie* obvious. (See, *In re* Ratti, 270 F.2d 810, 123 USPQ 349 (CCPA 1959)).

In the instant case, the Examiner has proposed to combine the teaching of Does *et al.* with the teachings of Ishida *et al.* and Hiei *et al.*. However, such a modification of Does *et al.* would not only render it unsatisfactory for its intended purpose, but would also change its principle of operation. Specifically, the Examiner has cited Does *et al.*, as teaching a method of "obtaining one integrated T-DNA in the genome of tobacco 10 weeks after transformation by

using inverse polymerase chain reaction (IPCR) to amplify plant genomic DNA sequences flanking the known T-DNA sequences" (See, Office Action of June 25, 2004, pages 16-17). The method described in Does *et al.*, relies on the ability of a ***single*** inserted T-DNA containing construct to be excised and circularized by ligation followed by digestion by a restriction enzyme and inverse PCR. In contrast, both Ishida et al. and Hiei *et al.* rely on the use of a super binary vector that is comprised of ***two different plasmids***, where each construct includes T-DNA regions. (See, Ishida *et al.* page 749 and Hiei *et al.* page 272). In order to modify Does *et al.* to accommodate the presence of the second, and distinct, T-DNA containing plasmid, its principle of operation would necessarily have to be changed. Furthermore, the stated aim of Does *et al.*, "our aim was to obtain transgenic tobacco plants containing one integrated T-DNA copy per genome" would be frustrated by any such modification. (See, Does *et al.*, Abstract). In light of the foregoing, Applicants respectfully submit that the Examiner has failed to identify some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine references' teachings and therefore a *prima facie* case of obviousness has not been established. Accordingly, this provides a second, and independent, basis for finding that a *prima facie* case of obviousness has not been established.

Finally, Applicants note that Examiner has failed to establish that the proposed combination would have a reasonable expectation of success. Specifically, Applicants point out that the same reference identified by the Examiner as the motivation for one of skill in the art to combine the cited references, Ragot et al., actually establishes that one would not have a reasonable expectation of success in obtaining the claimed invention, as the following quotations make clear:

> "[p]roduction of fully converted isogenic lines through backcrossing procedures is a lengthy procedure, if at all possible (See Ragot *et al.*, page 45, first paragraph).
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> [t]herefore the true linkage drag value of the selected BC_4 is likely to be less than 1.3% of the genome (See, Ragot *et al.*, page 55, second paragraph).
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> [t]hese results clearly demonstrate that molecular markers provide important time and quality advantages over classical procedures for the production of near-isogenic lines through backcrossing (See, Ragot *et al.*, page 55,second paragraph)."

Taken together with the fact that an infinite number of backcrosses would be required to obtain a truly isotransgenic line, the combination of cited prior art demonstrate that the results would not have been expected. Applicants note that this provides a third, and fully independent, basis for finding that a *prima facie* case of obviousness has not been established.

Applicants also respectfully submit that contrary to the Examiner's view, Applicant's have not attacked references individually but have merely considered and broken down the teachings of each reference so as to demonstrate that when combined, the cited references do not render the present invention obvious. (For Examiner's view see, page 7 of the June 14, 2006 Office Action; pages 9-10 of the September 23, 2007 Office Action; and page 11 of the January 21, 2005 Office Action). The Examiner is requested to reconsider the rejection in light of the specific factual issues raised previously and herein and Applicants respectfully request that the rejections under 35 U.S.C. §103(a) be withdrawn.

2. The Claims Are Not Obvious Over Lundquist et al. In View Of Chyi et al.

Claims 18, 23-25, and 27 stand rejected under 35 U.S.C. §103(a) as unpatentable over Lundquist *et al.*, (US Patent No. 5,508,468, "Lundquist *et al.*"), in view of Chyi *et al.*, Mol

Gen Genet., 204:64-69, 1986 ("Chyi *et al.*"). In particular, the Examiner introduces the cited art and asserts the following rationale as establishing a *prima facie* case of obviousness:

> Lundquist et al teach a method for producing transgenic maize plants wherein said method comprises transforming cells of hybrid immature embryos, wherein said hybrid is produced by pollination of inbred line A188, a maize line suited for transformation, and inbred line B73, a maize line of interest (see column 17, line 49 to column 21, line 18 and Table 3).
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> Lundquist et al do not teach selection performed by isolation and identification of genomic sequences of the host adjacent to the T-DNA using RFLPs, backcrossing individuals to parental maize line of interest and selection of one transgenic individual obtained from the backcross.
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> Chyi et al teach using RFLPs to identify genomic sequences of the host adjacent to the T-DNA in tomato and backcrossing individuals to parental lines (see pages 65, 1st column, 3rd paragraph to 2nd column, end of 1st full paragraph). One of ordinary skill in the art would understand how to select at least one transgenic individual from a backcrossing method.
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> It would have been prima facie obvious to one of ordinary skill in the art at the time of Applicant's invention to combine the teachings of Lundquist et al with those of Chyi et al to produce an isotransgenic maize line.
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> One of ordinary skill in the art would have been motivated to combine these teachings because Lundquist et al teach '[g]enetic engineering of plants...offers considerable promise to modern agriculture and plant breeding' (see column 1, lines 22-26).
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> In addition, one of ordinary skill in the art would have a reasonable expectation of success based on the success of Lundquist et al in producing transgenic maize lines and the success of Chyi et al in using RFLPs to locate genomic sequences.

(See, Office Action of December 13, 2006, pages 6-7)

As a preliminary matter, Applicants respectfully point out that the Examiner appears to be improperly using hindsight to reconstruct the claimed invention using the Applicants' disclosure as a blueprint. In particular, Applicants point out that the Examiner has cherry-picked references that have no relation to the instant invention but that disclose general ideas related to recombinant DNA technology. The Examiner has then argued that these disparate references can be combined to render the instant invention obvious. For example, the Examiner has identified Lundquist *et al.* as teaching a method of producing transgenic maize plants. (See, Office Action of December 13, 2006, pages 6-7). However, the Examiner fails to

note that the only method used by Lundquist *et al.* is microparticle bombardment, which is completely unrelated to the Agrobacterium-mediated introduction of transgenes disclosed in the current claims. In addition, the Examiner fails to note that Lundquist *et al.* actually argues against the use of Agrobacterium-mediated methods, pointing out that such a system may not even work in maize.[3] Similarly, the Examiner attempts to combine Lundquist *et al.* with Chyi *et al.*, a reference directed to the genetic manipulation of tomato plants. The success or failure of a transformation system in tomato plants, which the authors describe as "an ideal plant in which to test...[which is] readily amenable to transformation with Agrobacterium..." is wholly distinct from the currently claimed transformation of maize, which is characterized ***in the art cited by the Examiner*** as not readily amenable to transformation with Agrobacterium. (See, Chyi *et al.*, page 64.; Lundquist *et al.*, Column 2, Lines 5-10.) Accordingly, Applicants respectfully submit that neither Lundquist *et al.* or Chyi *et al.* provide any motivation to combine their respective teachings, and neither singly nor taken together, teach or suggest the presently claimed invention.

Applicants also note that, just as discussed above in connection with the rejection over Ishida et al. and its supporting references, the cited art in this rejection (either alone or in combination) does not teach or suggest the following claim limitation of Claim 18:

> b) selecting for at least one individual among said hybrid primary transformants which has said T-DNA integrated only into the genome of said line of interest, in order to obtain selected individual(s), wherein said selection is performed by isolation and identification of genomic sequences of the host adjacent to the T-DNA, using Restriction Fragment Length Polymorphism;

[3] See Lundquist *et al.*, Column 2, Lines 5-10: "A Graves et al., Plant Mol. Biol. 3, 43(1986) reported Agrobacterium-mediated transformation of [maize] seedlings. The evidence was based upon assays which can sometimes be unreliable. To date, there have been no further reported successes with pollen and Agrobacterium-mediated transfer techniques"

The Examiner appears to contend that that Chyi *et al.* teaches such a selection method, suggesting that the cited reference teaches "using RFLPs to identify genomic sequences of the host adjacent to the T-DNA in tomato and backcrossing individuals to parental lines." (See, Office Action of December 13, 2006, page 6, citation removed). However, in making this assertion, the Examiner has not considered the claim limitation as a whole. Specifically, the Examiner has not identified a means taught or suggested by Chyi *et al.* to select a specific individual among the hybrid primary transformants, wherein the specific individual contains the T-DNA integrated within a chromosome originating from the line of interest. Without this step, as discussed above, it would be impossible to predict that the subsequent backcrosses would generate an isotransgenic maize line as claimed. Given the deficiency in the Examiner's position, and the Examiner's admission that Lindquist *et al.* fails to provide any such teaching or suggestion, Applicants respectfully assert that the cited art fails to teach or suggest all of the claim limitations. Applicants note that this provides a third, and fully independent, basis for finding that a *prima facie* case of obviousness has not been established.

In light of the foregoing, the Examiner is requested to reconsider this rejection under 35 U.S.C. §103(a) and Applicants respectfully request that it be withdrawn.

CONCLUSION

Applicants believe that in light of the foregoing amendments and remarks, the claims are in condition for allowance, and accordingly, respectfully request withdrawal of the outstanding objections and rejections. The Examiner is kindly invited to contact the undersigned if helpful to advance the application to allowance, which is earnestly sought.

Respectfully submitted,

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